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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,505	03/19/2004	Rosa Cuberes Altisen	785-011733-US (PAR)	7668

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EXAMINER	
FREISTEIN, ANDREW B	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,505	ALTISEN ET AL.	
	Examiner	Art Unit	
	Andrew B. Freistein	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-17 and 23-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-12,23-28 and 36-42* is/are allowed.

6)☒ Claim(s) *13,15-17 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20060620*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 5/24/2006 has been entered. Claims 1-13, 15-17, 23-42 are pending in the instant application. Claims 14 and 18-22 were cancelled.

Restriction Requirement

Group I, claims 1-10, are now in condition for allowance. As a result, Groups II-IV are rejoined and the restriction requirement is withdrawn.

Claim Rejections - 35 USC § 102

Claims 1, 2, 4-7 and 23 were rejected under 35 U.S.C. 102(a) as being anticipated by Otani et al., "An Evaluation of Amide Group Planarity in 7-Azabicyclo[2.2.1]heptane Amides. Low Amide Bond Rotation Barrier in Solution," J. Am. Chem. Soc., Vol. 125(49) pp .15191-15199 (2003). As a result of the amendment filed 5/24/2006, the rejections were overcome and are withdrawn.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-17 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting COX-1/COX-2 *in vitro*, having analgesic activity *in vivo* in rats, having activity against Edema in vivo in rats, having antiarthritic activity in rats, and showing PGE2 production in rats, the specification does not reasonably provide enablement for the prophylaxis and/or

treatment of all cyclooxygenase-1 or cyclooxygenase-2 related disorders (claim 13), the prophylaxis and/or treatment of all pain (claim 15), the prophylaxis and/or treatment of all inflammation and inflammation disorders (claims 16-17), the prophylaxis and/or treatment of angiogenesis mediated disorders (claim 29), the prophylaxis and/or treatment of cancer (claim 30), the prophylaxis and/or treatment of gastrointestinal disorders (claim 31), the prophylaxis and/or treatment of skin related conditions (claim 32), the prophylaxis and/or treatment of bronchitis, tendinitis and bursitis (claim 33), the prophylaxis and/or treatment of fever (claim 34), and the prophylaxis and/or treatment of polyps (claim 35). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The state of the prior art;
4. The relative skill of those in the art;
5. The predictability or unpredictability of the art;
6. The amount of direction or guidance presented [by the inventor];
7. The presence or absence of working examples; and
8. The quantity of experimentation necessary [to make and/or use the invention].

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

The Nature of the Invention

The instant application is drawn to a compound of formula (I), a process for preparing a compound of formula (I), a medicament comprising a compound of formula (I), and a method for the prophylaxis and/or treatment of a pain, inflammation, cancer, skin and gastrointestinal disorders comprising administering a compound of formula (I).

The Breadth of the Claims

Claims 13, 15-17 and 29-35 are drawn to the method for the prophylaxis and/or treatment of various disorders comprising administering to a patient in need thereof a compound of formula (I). Furthermore, the prophylaxis and/or treatment of all cyclooxygenase-1 or cyclooxygenase-2 related disorders (claim 13), the prophylaxis and/or treatment of all pain (claim 15), the prophylaxis and/or treatment of all inflammation (claims 16-17), the prophylaxis and/or treatment of angiogenesis mediated disorders (claim 29), the prophylaxis and/or treatment of cancer (claim 30), the prophylaxis and/or treatment of gastrointestinal disorders (claim 31), the prophylaxis and/or treatment of skin related conditions (claim 32), the prophylaxis and/or treatment of bronchitis, tendinitis and bursitis (claim 33), the prophylaxis and/or treatment of fever (claim 34), and the prophylaxis and/or treatment of polyps (claim 35) are all claimed in the instant application.

The State of the Prior Art

The state of the art is very high in terms of finding a chemical compound that has the desired effect on the particular receptor, the bioavailability, stability, ease of production, and limited unwanted side effects.

COX-1 and COX-2 inhibitors have been show to inhibit pain as nonsteroidal anti-inflammatory drugs. Specifically, mediciations that inhibit the activity of prostaglandins (PG) enzymes are prescribed to treat osteoarthritis and rheumatoid arthritis (Wallace et al., "Emerging roles for cyclooxygenase-2 in gastrointestinal mucosal defense," Br. J. Pharmacol., **145**, 275-282, 275 (2005)). However, COX-2 also cause significant ulceration and exhibit significant toxicity in the renal and cardiovascular systems. *Id.* In addition, studies have shown that the administration to rats of COX-1 and COX-2 inhibitors can cause damage to the GI track (Wallace, "COX-2: A Pivitol Enzyme in Mucosal Protection and Resolution of Inflammation," The Scientific World J., 6, 577-588, 578 (2006)).

The Relative Skill of Those in the Art

One of ordinary skill in the pharmaceutical arts is very high, i.e. a Ph.D. or M.D.

The Predictability or Unpredictability of the Art

The ability of preventing (prophylaxis) and pain, inflammation, cancer, skin and gastrointestinal disorders all with one compound is not known in the art. The burden of enabling one skilled in the art to prevent and treat these diseases is much greater than that of showing activity for COX-1/COX-2 *in vitro* in human blood samples. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing or treating all of these diseases. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for treating these diseases.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified actives could actually treat all of these disease by simply administering, by any method, an amount of the claim specified compound. Furthermore, the specification fails to enable one of ordinary skill in the art to produce a chemical compound that has the required bioavailability, stability, formulation, ease of purification, hydroscopicity, recovery, etc. Thus, the specification fails to enable one of ordinary skill in the art how to make the desired compound and the method of using it in seven different ways.

The Amount of Direction or Guidance

The specification provides COX-1/COX-2 enzyme assays, COX-1/COX-2 activity in human blood samples, analgesic activity *in vivo* in rats, activity against Edema *in vivo* in rats, antiarthritic activity in rats, and PGE2 production in rats. The enzyme assays are cellular *in vitro* assays that merely provide data in a limited controlled environment.

The Presence or Absence of Working Examples

The specification provides no working examples of treatment of prophylaxis or treatment of pain, inflammation, cancer, skin and gastrointestinal disorders.

The Quantity of Experimentation Necessary [to Make and/or Use the Invention]

The quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant

method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing caner, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue. Therefore, claims 13, 15-17 and 29-35 are rejected under 35 U.S.C. § 112, 1st paragraph.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew B. Freistein whose telephone number is (571) 272-8515. The examiner can normally be reached Monday-Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Andrew B. Freistein
Patent Examiner, AU 1626

Joseph K. McKane
Supervisory Patent Examiner, AU 1626
Date: June 20, 2006